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Summary Review of the Health Effects Associated with Propylene Oxide Health Issue Assessment

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16. ABSTRACT

Propylene oxide's major use is as an intermediate in the production of polyurethane foams and propylene glycol. Average atmospheric concentrations at a distance of 20 km or greater from production facilities are estimated to be less than 0.001 ppt (10^{-7} ppb). The calculated atmospheric halflife is 6.1 days. Propylene oxide is likely to be readily absorbed through the gastrointestinal and respiratory tracts. The LC_{50} for a 4-hour inhalation exposure was 9486 mg/m^3 in rats and 4126 mg/m^3 in mice. The lowest concentrations at which effects were seen in experimental animals with acute or subchronic exposures were in the range of approximately 400 to 500 ppm propylene oxide. The no-observed-adverse-effect level for prolonged repeated 6- to 7-hour daily exposure is 70 mg/m^3. The published literature shows evidence for carcinogenic and genotixic effects. The NTP carcinogenicity study which exposed rats and mice to propylene oxide concentrations of 200 to 400 ppm showed evidence of carcinogenicity. Propylene oxide is tentatively placed in the B-2 (probable human carcinogen) category of the Agency's classification of carcinogenicity evidence because of the positive animal data and the absence of epidemiological studies. Limited information on air concentrations indicate typical annual average ambient air concentrations for propylene oxide of $\leq$ 1 ppt.

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Abstract

Propylene oxide's major use is as an intermediate in the production of polyurethane foams and propylene glycol. Average atmospheric concentrations at a distance of 20 km or greater from production facilities are estimated to be less than 0.0001 ppt (10^{-7} ppb). The calculated atmospheric half-life is 6.1 days. Propylene oxide is likely to be readily absorbed through the gastrointestinal and respiratory tracts. The LC_{50} for a 4-hour inhalation exposure was 9486 mg/m^3 in rats and 4126 mg/m^3 in mice. The lowest concentrations at which effects were seen in experimental animals with acute or subchronic exposures were in the range of approximately 400 to 500 ppm propylene oxide. The no-observed-adverse-effect level for prolonged repeated 6- to 7-hour daily exposure is 70 mg/m^3 (29 ppm). The published literature shows evidence for carcinogenic and genotoxic effects. The NTP carcinogenicity study which exposed rats and mice to propylene oxide concentrations of 200 to 400 ppm showed evidence of carcinogenicity. Propylene oxide is tentatively placed in the B-2 category of the Agency's classification system for carcinogenicity evidence because of the positive animal data together with the absence of epidemiological studies. Limited information on air concentrations indicates typical annual average ambient air concentrations for propylene oxide of ≤ 1 ppt.

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1. Background Information

This overview provides a brief summary of the data available on the health effects of exposure to propylene oxide. Emphasis is placed on determining whether there is evidence to suggest that propylene oxide exerts effects on human health under conditions and at concentrations commonly experienced by the general public. Both acute and chronic effects are addressed, including general toxicity, teratogenicity, mutagenicity, and carcinogenicity. To place the health effects discussion in perspective, this report also summarizes air quality aspects of propylene oxide in the United States, including sources, distribution, fate, and concentrations associated with certain point sources.

1.1. CHEMICAL CHARACTERIZATION AND MEASUREMENT

Propylene oxide (CAS No. 75-56-9) belongs to a class of ethers known as the epoxyalkanes. It is a colorless liquid at ambient temperatures with a molecular weight of 58.08. It is very soluble in water (405 g/l @ 20°C) and has a low density (0.825 g/ml @ 25°C) and a high vapor pressure (445 torr @ 20°C) (Windholz et al., 1983; Hawley, 1981; Weast, 1984).

Propylene oxide released into the environment may be measured by a variety of analytical methods. These include spectrophotometry, gas chromatography, electron impact spectroscopy, and colorimetric methods (International Agency for Research on Cancer, 1976). A multigas analyzer utilizing microwave spectroscopy has also been developed to monitor propylene oxide in air (Kirk and Dempsey, 1982).

The method of the National Institute for Occupational Safety and Health for analysis of propylene oxide in air involves the adsorption of the compound on activated charcoal in a sampling tube, desorption with carbon disulfide, and analysis using a gas chromatograph equipped with a flame ionization detector. The method has been validated over the range of 121-482 mg/m^3 using a 5-liter sample. The average value obtained with this method was 94.4 percent of the concentration (240 mg/m^3) analyzed.

Russell (1975) discussed the use of gas chromatography with flame ionization detection for the analysis of propylene oxide in air. This method uses sampling tubes packed with a porous polymer gas chromatographic adsorbent (Porapak N) to collect the propylene oxide. The collected compound is then thermally desorbed directly into the gas chromatograph for analysis. Recovery is 100 ± 3 percent for samples analyzed up to 3 weeks after collection. This technique is most appropriate for concentrations of less than 100 ppm in a 1-liter air sample, and has a sensitivity of approximately 1 ppb.

A method for the determination of propylene oxide in air has also been reported by Gronsberg (1981). The method is based on the hydrolysis of propylene oxide to form propylene glycol, which is then oxidized to formaldehyde with periodic acid and determined photometrically following reaction with chromotropic acid. The detection limit of the method is 1 µg, and the minimum measurable concentration is 0.5 mg/m^3.

Gas chromatography may also be used to determine the levels of propylene oxide in food, cellulose, and plastic products (International Agency for

Research on Cancer, 1976). Methods for the analysis of propylene oxide in water were not reported in the available literature.

1.2. ENVIRONMENTAL RELEASE, TRANSFORMATION AND EXPOSURE

Of the top 50 chemicals ranked by U.S. production volume, propylene oxide was 44th in 1980 with a total production volume of 1.77 billion pounds (Storck, 1981). Propylene oxide is manufactured at four locations in the Gulf Coast region of the United States by Dow Chemical USA and ARCO Chemical Company. The total combined capacity, including the scheduled 1984 expansion by ARCO, is approximately 3 billion pounds (SRI International, 1984).

The major use of propylene oxide is in the production of polyether polyols, the primary component of polyurethane foams, and in the production of propylene glycol. Smaller amounts are used in the fumigation of foodstuffs and plastic medical instruments and in the manufacture of dipropylene glycol and glycol ethers, or as pesticides (International Agency for Research on Cancer, 1976).

Propylene oxide has also been reported to be an effective soil sterilant (Skipper and Westermann, 1973) but is not used commercially to sterilize soil.

The major release of propylene oxide is expected to occur into the atmosphere during its production or use as an intermediate or as a fumigant and a sterilant. The distribution of released propylene oxide into the environmental compartments has not been reported. Estimates for the analog ethylene oxide indicate that 95 percent is released into air, 2 percent into water, and 3 percent into deep wells (Brown et al., 1975).

It has been estimated that 1.3 million pounds of propylene oxide is released into the atmosphere annually (Anderson, 1983). Based on model plant analyses, levels of propylene oxide emissions from various production processes have been determined (Table 1-1). These levels are intended to represent typical emissions from a well-designed and well-operated plant without specific emission control devices other than those for economy and safety (Peterson, 1980).

Data from a 1983 emissions inventory for four manufacturing plants that use propylene oxide in the Philadelphia, PA, area report that a total of 849 pounds of propylene oxide is released from these plants each year (production volumes not stated) (Lazenka et al., 1983).

The only available information on atmospheric concentrations of propylene oxide is estimates of levels in the vicinity of propylene oxide production plants. The annual average atmospheric concentration at a distance of 20 km or greater from production plants was estimated to be less than 0.0001 ppt (10^{-7} ppb) (Anderson, 1983). The only available data on water concentrations are measurements from the discharge pipe of an epoxyalkane production plant on the Ohio River. The measured concentration of propylene oxide at the discharge pipe from this plant was 0.047 mg/l (STORET, 1980). However, due to substantial dilution in the Ohio River, actual downstream concentrations would be expected to be much lower.

Tolerance levels for propylene oxide in foods have been set by the Food and Drug Administration. A maximum allowable concentration of 700 mg/kg (as propylene glycol) has been established for fruits and 300 mg/kg for cocoa, gums, nutmeats, spices, and starch (Code of Federal Regulations, 1985a).

Propylene oxide has been detected in food products fumigated with a 1:4 propylene oxide:carbon dioxide mixture. Levels of 4147 and 5910 mg/kg were found in lard and oleic acid, respectively, 24 hours after fumigation. Propylene oxide residues as high as 2000 mg/kg were also detected in various plastic and

Table 1-1. Propylene Oxide Emissions by Process Type

Production Process	Plant Capacity, 1000 metric tons/yr	Propylene oxide emissions	
		g/kg[a]	kg/hr
Chlorohydrination	68	0.0549	0.8365
Isobutane hydroperoxide	417	0.0217	1.0300
Ethylbenzene hydroperoxide	181	0.0005	0.0100

[a] Grams of emissions per kilogram of propylene oxide produced.
Source: Peterson (1980).

cellulose products used for food storage up to 3 hours following fumigation (International Agency for Research on Cancer, 1976).

Analysis of wheat fumigated with propylene oxide indicated levels of several hundred parts per million of propylene glycol. Propylene oxide can also combine with the natural inorganic chloride content of foodstuffs, forming propylene chlorohydrin, which is toxic and persistent under food processing conditions (Lindgren et al., 1968).

Propylene oxide has also been detected as one of the volatile organic compounds produced from plastics during a test simulating an electrical circuit overheat situation. The test was conducted at 250°C to simulate real-life electrical overload conditions (Rigby, 1981).

Occupational exposures to propylene oxide have also been reported. NIOSH (1977) estimated that about 270,000 workers are occupationally exposed to propylene oxide in the United States. OSHA (Code of Federal Regulations, 1985b) and The American Conference of Governmental Industrial Hygienists (ACGIH) have established limits on atmospheric concentrations of propylene oxide in the workplace. OSHA has set an 8-hour TWA of 100 ppm (240 mg/m^3), whereas The ACGIH (1984) recommends a TLV-TWA of 20 ppm (50 mg/m^3) over an 8-hour period.

Typical average daily occupational exposure to propylene oxide in 1979 was 2 ppm for workers involved in its production and storage. Peak exposures in 1979 ranged as high as 3,800 ppm (about 9,000 mg/m^3); however, with proper engineering controls, these peak levels have been reduced to less than 1 ppm (2.37 mg/m^3; Flores, 1983). Results of a four-plant sampling program by BASF Wyandotte Corporation indicated propylene oxide levels ranging from less than 0.18 to 20.3 mg/m^3 with an average concentration of 1.53 mg/m^3 (McClellan, 1979).

Propylene oxide may be released into the atmospheric and aquatic compartments of the environment from point sources such as manufacturing plants and from numerous nonpoint sources such as areas where products are treated. Accidental loss may also occur during transport, handling, and storage. Propylene oxide released into the environment is expected to be very mobile due to its water solubility, high volatility, and leachability, although degradative processes will probably limit its transport.

The atmospheric fate and residence time for propylene oxide has been reported by Cupitt (1980). A measured rate constant for the OH radical reaction of 1.3×10^{12} cm^3/molecule-sec has been reported. The calculated atmospheric residence time is 8.9 days with a half-life of 6.1 days. Expected

degradation products include $CH_3C(O)OCHO$, $CH_3C(O)CHO$, formaldehyde (H_2CO), and $HC(O)OCHO$.

Products identified from free-radical reactions of propylene oxide initiated by ultraviolet light include acetone, isopropyl alcohol, propionaldehyde, and propyl alcohol (Gritter and Sabatino, 1964).

In water, propylene oxide hydrolyzes under environmental conditions to form propylene glycol (Long and Pritchard, 1956), which is highly soluble and relatively less toxic than propylene oxide. The estimated hydrolysis half-life of propylene oxide in water at pH 5-9 (25°C) ranges from 7 to 12 days (Zafran et al., 1980).

Propylene oxide also reacts readily with chloride ions. The estimated half-life for this reaction indicates that this is an important degradative process in water with high chlorine concentrations, such as seawater. Similar reactions appear to occur in food products and medical equipment sterilized with propylene oxide. The half-lives of these reactions in water at pH 5-9 are as follows: freshwater, 6170-8440 days; estuarine, 4.2-6.2 days; and seawater, 3.3 days (Zafran et al., 1980).

Biodegradation data suggest that propylene oxide is not very readily biodegradable. A 5-day BOD removal rate of 17 percent, a COD value of 1.77, and a theoretical oxygen demand of 2.21 were reported by Bridie et al. (1979b). According to the degradability index (ratio of 5-day BOD to COD) of Lyman et al. (1982), propylene oxide is considered "relatively undegradable."

The log octanol/water partition coefficient for propylene oxide was reported to be -0.13 (Radding et al., 1977). Because of its low log P value and moderate to rapid biological and chemical degradation, it is not expected to bioconcentrate or bioaccumulate.

Based on the equation of Briggs (1973), propylene oxide can be classified as very mobile in soil. Thus, it is expected that releases of the compound to the soil would be readily transported to air or water.

1.3. ENVIRONMENTAL EFFECTS

The available literature on the ecological effects of propylene oxide is very limited. No information was found on the effects of propylene oxide on aquatic plants, invertebrates, micro-organisms, or terrestrial plants. In addition, no chronic or life-cycle effects on ecological species have been reported. Chronic effects would not be expected, since propylene oxide is water-soluble, leachable, and volatile, and reacts with water; in addition, it is hydrolyzed into other water-soluble substances and is not expected to persist, bioconcentrate, or bioaccumulate.

Limited data were found on the acute toxicity of propylene oxide to fish and its effects on soil chemistry. For freshwater fish, the 96-hour LC_{50} values were 141 mg/l for the mosquito fish (*Gambusia affinis*) and 215 mg/l for the bluegill (*Lepomis macrochirus*) (Crews, 1974). The 24-hour LC_{50} for goldfish (*Carassius auratus)* was 170 mg/l (Bridie et al., 1979a). For marine fish, the 96-hour LC_{50} for mullet (*Mugil cephalus*) was 89 ppm (Crews, 1974).

Sterilization of three types of soil with propylene oxide resulted in pH changes and increased concentrations of some of the available plant nutrients (Skipper and Westermann, 1973). The pH increased by 0.5-0.8 units after treatment. These increases were attributed to reactions of propylene oxide with labile H-atoms in the organic and inorganic fractions of the soil. There were also increases in extractable manganese levels in two soil types and an increase in extractable nitrogen in one; however, the pattern of change was not consistent among the three soils. Available phosphorus concentrations increased in one soil, but not in the second, and were not tested in the third soil

because of its high initial phosphorus content. Treatment with propylene oxide did not affect either extractable potassium or extractable calcium levels in any of the tested soils. The increases in some of the nutrient concentrations in certain soils were attributed to either the solubilization of inorganic forms or the release from organic matter or microbial cells.

2. Health Effects

2.1. PHARMACOKINETICS AND METABOLISM

No studies were identified in the literature on the absorption, distribution, metabolism, or excretion of propylene oxide. Several studies were found on the interaction of propylene oxide with cellular constituents that provide information on the behavior of propylene oxide at the cellular level. These studies are discussed below. In the absence of data on the metabolism of propylene oxide, data are presented on structurally similar compounds such as propylene, epichlorohydrin, and other epoxides. The data provide some information on the possible uptake and metabolism of propylene oxide, since it is expected that propylene oxide would behave similarly to these compounds.

The kinetics of the uptake of inhaled propylene were investigated by Svensson and Osterman-Golkar (1984), whose data suggested that propylene is rapidly metabolized to propylene oxide. In this study, groups of 15 male CBA mice (average weight 31 g) were placed in closed, all-glass, 11-liter inhalation chambers filled with propylene atmospheres ranging in concentration from 95 to 1715 ppm. The depletion of propylene from the chamber was monitored by gas chromatography at regular intervals over a period of time equivalent to at least one half-life. The results indicated that the uptake process was saturable and enzymatic over the tested range (i.e., resulting from metabolism) and followed Michaelis-Menton kinetics. The authors calculated the K_m and V_{max} to be 800 ± 600 ppm and 8 ± 0.5 mg (kg body weight)$^{-1}$hr^{-1}, respectively. In a second experiment, Svensson and Osterman-Golkar exposed 12 mice to ^{14}C-labeled propylene for 1 hour and looked for the binding of label to hemoglobin and DNA from the liver, testes, spleen, lungs, and kidneys. They identified labeled amino acids and guanine and attributed the label to the metabolism of propylene to propylene oxide and subsequent alkylation of proteins and DNA.

The absorption, distribution, and metabolism of epichlorohydrin have been thoroughly investigated. Epichlorohydrin differs from propylene oxide in that the former has a chlorine-bearing C-3 carbon and hence two electrophilic reactive sites (the halogenated carbon and the C-1 carbon of the epoxide ring), whereas propylene oxide has one.

Studies in rats have indicated that epichlorohydrin is readily absorbed after oral or inhalation exposures. Weigle et al. (1978) conducted a distribution study in Charles River CD rats that were administered 10 mg/kg labeled epichlorohydrin by oral gavage; peak tissue concentrations were found 2 hours after dosing. Label from the epichlorohydrin was distributed to the kidneys, liver, pancreas, adrenals, and spleen in descending order of the tissue concentration of label. Male Fischer 344 rats were administered 1 or 100 mg/kg labeled epichlorohydrin by gavage or by inhalation (Smith et al., 1979). Administration by both routes resulted in a dose-related absorption of the label; at 72 hours after dosing, 46-54 percent of the label had been excreted in the urine and 25-42 percent was exhaled as carbon dioxide regardless of the dose or route. Smith et al. reported the distribution of label 3 hours after a single oral dose of 100 mg/kg epichlorohydrin and after a 6-hour inhalation exposure at 100 ppm. After the oral dose, the highest levels of label were in the stomach, small

intestine, kidneys, and large intestine. After inhalation, the highest levels were found in the nasal turbinates, lacrimal glands, kidneys, large intestine, and liver.

A metabolic pathway for epichlorohydrin was proposed by Fakhouri and Jones (1979). In the proposed pathway, the primary route of detoxification is by conjugation with glutathione, with the end products being N-acetyl-S-(2,3-dihydroxypropanol) cysteine and 1,3-(bis-N-acetyl cysteinyl) propan-2-ol. Jones and O'Brien (1980) performed a similar study and proposed an alternative pathway in which epichlorohydrin is hydrolyzed via epoxide hydrase and then phosphorylated to form 3-chloroglycerophosphate or oxidized to beta-chloro-lactate and oxalate.

In general, it is expected that the metabolism of propylene oxide in rodents would be similar to that of other epoxides; i.e., it is likely to be readily absorbed through the gastrointestinal and respiratory tracts and distributed to the kidneys, liver, pancreas, adrenals, and spleen. Excretion is likely to be via the urine and expired air, which would involve conjugation with glutathione and conversion to carbon dioxide, respectively.

2.2. BIOCHEMICAL EFFECTS

Three *in vitro* studies were conducted on the interaction of propylene oxide with subcellular constituents, primarily nucleotides and DNA. Lawley and Jarman (1972) found that propylene oxide reacts with DNA under physiological conditions (neutral pH) to form two alkylated adducts, identified as 7-(2-hydroxypropyl) guanine and 3-(2-hydroxypropyl)adenine. The molar ratio of the products 3-alkyladenine and 7-alkylguanine was found to be 1:5. The yield was relatively low compared to the high concentrations of reagents used; e.g., 16 mM-DNA P incubated with 230 mM-propylene oxide for 7 days gave 6.2 mmol of 2-hydroxypropyl/mol of DNA P; similarly, 7-alkylguanine gave 33 mmol of the 2-hydroxypropyl derivative/mol of DNA P. These adducts hydrolyze out of the alkylated DNA at neutral pH values at 37°C. The order of reactivity of the various ring-N atoms of adenine was N-3 > N-1 >N-9; no evidence for reaction at N-7 was found, whereas guanosine was alkylated at N-7. It was suggested that product formation indicated a bimolecular reaction mechanism, binding to the N-7 of guanine and the N-3 of adenine.

Hemminki and Vainio (1980) studied the *in vitro* alkylation of guanosine and deoxyguanosine (nucleotides) by epoxides and glycidyl ethers. Propylene oxide was found to be one of the least active alkylating agents, having an alkylation rate that was 28 percent of the most reactive compound, phenyl glycidyl ether; other data were not presented. It was also found that epoxides, including propylene oxide, alkylate deoxyguanosine faster than single-stranded DNA, at equal concentrations of guanine (Hemminki, 1979). In another study, Hemminki et al. (1980) characterized the reaction products of a series of epoxides with deoxyribonucleosides in order to investigate whether differences in adduct formation would explain the differential mutagenic potency of the epoxides. The reactions were conducted at near-saturation conditions for 3 hours in order to identify the products, and thus reaction rates were not determined. Propylene oxide reacted with N-7 of deoxyguanosine to yield one product, and with N-6 of deoxyadenosine to yield one major reaction product.

Farmer et al. (1982) conducted an *in vivo* study to determine if exposure to propylene oxide would produce measurable levels of alkylated hemoglobin. Female LAC Porton-derived Wistar rats (170-200 g body weight) were exposed by inhalation to propylene oxide at 0-2000 ppm (four animals per dose) for 4 hours. After exposure, hemoglobin was isolated from red blood cells and hydrolyzed; the amino acids were separated by thin-layer chromatography, and the level of N-3'-(2-hydroxypropyl)histidine, an

alkylation product of the protein, was then quantified. A linear dose-related increase in alkylation, with a maximum of 10.5 µg of the histidine derivative, was found per gram of hemoglobin. The authors suggested that measurement of hemoglobin alkylation could be developed as an assay to monitor worker exposure to propylene or propylene oxide.

2.3. ACUTE TOXICITY

Several studies have been conducted to determine the acute effects of propylene oxide. The acute toxicity values (LD_{50}, LC_{50}, and LC_{Lo}) are presented in Table 2-1.

Rowe et al. (1956) reported the acute effects of propylene oxide following oral administration in female rats, skin contact in rabbits, and inhalation in female rats and guinea pigs. In female rats, single oral doses of 1.0 g/kg resulted in 100 percent mortality while no deaths occurred at 0.3 g/kg.

In rabbits, skin contact with undiluted propylene oxide and with 10 and 20 percent aqueous solutions resulted in hyperemia and edema following exposure for 6 minutes or longer (Rowe et al., 1956). The intensity of response increased with increasing exposure time. Some evidence indicated that the diluted solutions were more irritating than the undiluted ones.

Female rats and guinea pigs exposed to propylene oxide vapors at concentrations ranging from 2,000 to 16,000 ppm for 0.25-7 hours showed irritation of the respiratory passages and eyes as well as weight loss (Rowe et al., 1956). In rats, no effects were noted after single exposures at 1000 ppm for 7 hours, 2000 ppm for 2 hours, or 4000 ppm for 0.5 hour.

The NTP (National Toxicology Program, 1985) reported results of single 4-hour exposure inhalation studies of propylene oxide using F344/N rats and $B6C3F_1$ mice of both sexes. The calculated acute toxicity values are listed in Table 2-1. Rats (five animals/sex/dose) were exposed to propylene oxide concentrations of 1277, 2970, 3794, and 3900 ppm (3033, 7055, 9012, and 9204 mg/m^3), with mortalities of 0/5, 1/5, 4/5, and 3/5 for the males and 0/5, 2/5, 4/5, and 3/5 for the females, respectively. Clinical observations in animals exposed at the three higher concentrations included dyspnea and red nasal discharge.

Male and female mice (five animals/sex/dose) were exposed to propylene oxide concentrations of 387, 859, 1102, 1277, and 2970 ppm (919, 2041, 2618, 3033, and 7054 mg/m^3), with mortalities of 0/5, 0/5, 2/5, 2/5, and 5/5 for the males and 1/5, 0/5, 4/5, 5/5, and 5/5 for the females. Dyspnea occurred in animals of all groups; narcosis was observed in animals exposed to the two highest doses, and lacrimation occurred in animals exposed to the highest dose (National Toxicology Program, 1985).

2.4. SUBCHRONIC TOXICITY

Following repeated oral doses in female rats (18 doses in 24 days), a slight loss of body weight, gastric irritation, and slight liver damage were seen at 0.3 g/kg; no effects were noted at the 0.2 or 0.1 g/kg levels (Rowe et al., 1956).

Rowe et al. also reported the results of subchronic inhalation studies with rats, guinea pigs, rabbits, and monkeys (Table 2-2). No toxic effects were observed following repeated exposure to propylene oxide vapor at 195 ppm for 128-154 7-hour exposures. In one experiment using a 457-ppm exposure level, growth of guinea pigs and rats was suppressed after 25-27 7-hour exposures over 37-39 days. At the same exposure level, after 79-138 7-hour exposures, some rats developed pneumonia and died; and after 110 7-hour exposures, guinea pigs showed eye and respiratory tract irritation as well as slight growth depression, but no deaths occurred.

Table 2-1. Acute Toxicity Values for Propylene Oxide

Species/strain (sex)	Route	Exposure protocol	Acute toxicity value	Reference
Mouse/NR[a] (M)	Oral	NR	LD_{50} 630 mg/kg	Antonova et al.,1981
Rat/Wistar (M)	Oral	NR	LD_{50} 1140 mg/kg	Smyth et al.,1941
Rat/NR	Oral	NR	LD_{50} 930 mg/kg	Smyth et al.,1970
Rat/NR (M/F)	Oral	NR	LD_{50} 520 mg/kg	Antonova et al.,1981
Rat/NR (F)	Oral	NR	LD_{50} 540 mg/kg	Antonova et al.,1981
Guinea Pig (M,F)	Oral	NR	LD_{50} 690 mg/kg	Smyth et al.,1941
Guinea Pig (M)	Oral	NR	LD_{50} 660 mg/kg	Antonova et al.,1981
Mouse/NR (M)	Inhalation	7 doses, 10 mice/dose	LC_{50} 4126 mg/m^3/4 hr	Jacobson et al.,1956
Mouse/B6C3F$_1$	Inhalation	5 doses, 5 mice/dose	LC_{50} 3540 mg/m^3/4 hr[c]	NTP, 1985
Mouse/B6C3F$_1$	Inhalation	5 doses, 5 mice/dose	LC_{50} 2420 mg/m^3/4 hr[c]	NTP, 1985
Rat/NR (M)	Inhalation	6 doses, 10 rats/dose	LC_{50} 9486 mg/m^3/4 hr	Jacobson et al.,1956
Rat/F344/N (M)	Inhalation	4 doses, 5 rats/dose	LC_{50} 8265 mg/m^3/4 hr[c]	NTP, 1985
Rat/F344/N (F)	Inhalation	4 doses, 5 rats/dose	LC_{50} 7697 mg/m^3/4 hr[c]	NTP, 1985
Guinea Pig (F)	Inhalation	2 doses,5 or10pigs/dose	LC_{Lo} 9486 mg/m^3/4 hr	Rowe et al., 1956
Dog/Beagle (M)	Inhalation	4 doses, 3 dogs/dose	LC_{Lo} 4750 mg/m^3/4 hr	Jacobson et al.,1956
Rabbit/NR	Dermal	NR	LD_{50} 1.5 mL/kg	Smyth et al.,1969

A subchronic inhalation study in male and female Cpb:WU rats indicated that exposure to propylene oxide at 600 ppm for 6 hours/day for 3 months caused decreased weight gain and degenerative and hyperplastic epithelial changes in the nasal passages (Reuzel and Kuper, 1983). At 300 ppm, there was slight growth retardation. This study was used to set levels for a life-time study in rats.

2.5. CHRONIC TOXICITY

Reuzel and Kuper (1983) performed an inhalation chronic toxicity/oncogenicity study in which groups of 100 male and 100 female Cpb:WU Wistar rats were exposed to propylene oxide at 0, 30, 100, or 300 ppm for 6 hours/day, 5 days/week for 123 weeks (females) or 124 weeks (males). Ten rats/sex/group were sacrificed at 12, 18, and 24 months. There were

Table 2-2. Results of Subchronic Inhalation Exposure to Propylene Oxide in Rats, Guinea Pigs, Rabbits, and Monkeys

Species/Sex	Vapor conc., ppm	No. of 7-hour Exposures	Mortality	Pathologic findings
Rat/M,F	102	138	9/40	None
Guinea pig/M,F	102	128	0/16	None
Rat/M,F	195	138	7/40	None
Guinea pig/M,F	195	128	0/16	None except lungs of females; slightly heavy
Rabbit/M,F	195	154	0/4	None
Monkey/F	195	154	0/2	None
Rat/M	457	79	5/10	Eye and respiratory irritation; growth depression; increased mortality; lung injury
Rat/F	457	138	7/10	Eye and respiratory irritation; growth depression; increased mortality; lung injury
Guinea pig/M	457	110	0/8	Eye and respiratory irritation; growth depression; slight liver injury
Guinea pig/F	457	110	0/8	Eye and respiratory irritation; growth depression; slight lung injury
Rabbit/M,F	457	154	0/2	None
Monkey/F	457	154	0/1	None

Source: Rowe et al. (1956).

considerable decreases in weight gain in both males and females exposed at 300 ppm propylene oxide during the first year of the study. However, the animals adapted and body weights were similar between control and dosed groups during the second year of the study. There was increased mortality in both males and females receiving 300 ppm propylene oxide as compared to controls, but no effects were noted in hematology, blood chemistry, or urinary parameters. At sacrifice, male rats exposed at 300 ppm had increased adrenal, spleen, liver, and lung weights as compared to controls, but there were no accompanying histopathologic changes in these organs. Histologic changes in the nasomaxillary turbinates of exposed rats were observed, consisting of degenerative changes in the olfactory epithelium and thickening of the submucosa and a dose-related increase in focal hyperplasia of the nasal epithelium. At 300 ppm, dilated renal tubules were found in the kidneys of 7 of 69 female rats but none was found in the controls. In addition, there was myocardial degeneration in 10 of 69 females at 300 ppm compared to an incidence of 3 of 69 in controls; 9 of 69 males at 300 ppm had thrombi in the heart, whereas the incidence in controls was 2 of 70. Preneoplastic changes were noted in that high-dose males also had prosoplasia in the exorbital lacrimal glands. Neoplastic findings are discussed in Section 2.7.

Lynch et al. (1984a) studied the chronic toxicity of inhaled propylene oxide in which groups of 80 male Fischer 344 rats were exposed to 0, 100, or 300 ppm propylene oxide vapor for 6.9 hours (average)/day, 5 days/week for 2 years

(488 days of exposure). There were significant decreases in mean body weights in rats exposed at 300 ppm from week 2 of the study and in rats exposed at 100 ppm from week 37 of the study. The median survival time was 700 days for controls, 705 days for rats exposed at 100 ppm, and 675 days for rats exposed at 300 ppm propylene oxide. For both groups of exposed rats, hemoglobin concentrations were elevated compared with controls. There were changes in differential leukocyte counts, but these changes were probably caused by outbreaks of *Mycoplasma* pneumonia at 8 and 16 months of the study. There were no dose-related changes in clinical chemistry or urinalysis parameters. At study termination, there were statistically significant increases in lung weights and lung-to-body weight ratios in both dosed groups, an increased adrenal-to-body ratio, and a decrease in testes weights and testes-to-body weight ratios in both dosed groups as compared to controls. The changes in the adrenals were correlated with histopathologic changes. Nonneoplastic histopathologic changes were seen in the respiratory system. There was a statistically significant increase in the incidence of chronic local pneumonia (66 of 80 and 53 of 80 at 100 and 300 ppm, respectively, compared to 6 of 79 in controls); edema of the lungs (6 of 80 and 11 of 80 at 100 and 300 ppm, respectively, compared to 0 of 79 in controls); suppurative rhinitis of the nasal cavity (21 to 77 and 44 of 78 at 100 and 300 ppm, respectively, compared to 12 of 76 in controls); complex epithelial hyperplasia of the nasal passages (11 of 78 at 300 ppm compared to 0 of 76 in controls); and an increased incidence of lymphoid hyperplasia in the tracheobronchial lymph nodes (41 of 76 and 41 of 79 at 100 and 300 ppm, respectively, compared to 3 of 73 in controls). Neoplastic changes in these rats are discussed in Section 2.7.

Renne et al. (1986) discussed the results of the National Toxicology Program (1985) studies. In this bioassay, F344/N rats and B6C3F$_1$ mice were exposed to propylene oxide vapors at concentrations of 200 or 400 ppm, 6 hours/day, 5 days/week for 2 years. Mean body weight decreased, when compared with that of control groups, during the second year of exposure in both mice and rats exposed to the higher dose (400 ppm) of propylene oxide. However, mean body weight at terminal sacrifice for rats exposed to 400 ppm was within 10% of chamber control group values. There was a decrease ($P < 0.005$) in survival at the end of the study in both male and female mice exposed to 400 ppm propylene oxide. Only 29 of 50 (58%) male mice and 10 of 50 (20%) female mice exposed to 400 ppm survived to terminal sacrifice, compared with 42 of 50 (84%) male control mice and 38 of 50 (76%) female control mice. No statistically significant trends in survival were observed among groups of male or female rats. The significant decrease in survival and body weight in mice exposed to 400 ppm propylene oxide indicates that chronic exposure to this concentration is toxic to mice. Neoplastic findings are discussed in Section 2.7.

The World Health Organization (1985) summarized the results of animal studies (excluding mutagenic, carcinogenic, and reproductive effects). They indicate a no-observed-adverse-effect level for prolonged repeated 6- to 7-hour daily exposure at a concentration of 70 mg/m^3 (29 ppm).

2.6. MUTAGENICITY

Propylene oxide was found to be mutagenic, causing base-pair substitutions in *Salmonella typhimurium* strains TA 100 and TA 1535 without S9 metabolic activation. The compound did not cause frameshift mutations in strains TA 1537, TA 1538, and TA 98 (Bootman et al., 1979; McMahon et al., 1979; Hemminki and Falck, 1979; Pfeiffer and Dunkelberg, 1980).

There was a dose-related increase in mutants at levels of propylene oxide between 40 and 1000 µg/ml in strain TA 100, when the assay was carried out in liquid culture in sealed tubes (1-hour incubation) and the cells plated and incubated in a sealed container. At 1000 µg/ml, there were 227 his^+ revertants/10^7 surviving bacteria (Bootman et al., 1979). Wade et al. (1978) reported that propylene oxide produced 166 his^+ revertants/µg in *Salmonella* strain TA 100 and 22 revertants/µg in strain TA 1535. Propylene oxide was also mutagenic without activation in spot tests in *Escherichia coli* strain WP2 (Bootman et al., 1979; Hemminki and Falck, 1979), *E. coli* strains CM891 (uvrA, pKM 101 plasmid) and CM871 (exr A^-, uvr A^-, rec A^-) (Bootman et al., 1979), and *Klebsiella pneumoniae* (Voogd et al., 1981). Migliore et al. (1982) reported that propylene oxide caused forward mutations (5 ade loci) in *Schizosaccharomyces pombe*, when the yeast was incubated for 6 hours in sealed test tubes with levels of propylene oxide between 3 and 30 mM. Mutation frequencies were similar in the absence and presence of an S9 mix. Kolmark and Giles (1955) found that propylene oxide caused reverse mutations in a purple adenine auxotrophic strain of *Neurospora*. In this test, reversion to adenine independence is usually accompanied by a lack of production of purple pigment. A maximum number of reversions was achieved by treating macroconidia with 0.5 M propylene oxide for 60 minutes. This produced 80 revertants/10^6 survivors and 27 percent survival.

Djuric et al. (1986) studied mutagenicity dose response for propylene oxides in *Salmonella typhimurium* tests systems TA100 and TA1535. Of three propylene oxides (propylene oxide, epichlorohydrin, and glycidol), propylene oxide produced the lowest dose-mutagenicity response. However, the fourth propylene oxide studied (trichloropropylene) produced inconsistent results.

Hardin et al. (1983b) tested propylene oxide for mutagenic activity in the *Drosophila* sex-linked recessive lethal test. Male flies were exposed statically to propylene oxide at 645 ppm (1530 mg/m^3) for 24 hours and mated with Muller-5(Basc) females on days 2-3 and 7-8 postexposure. F_1 females, heterozygous for the control or propylene oxide-treated, wild-type X-chromosome, were mated with Muller-5 males and cultures scored for wild-type F_2 males. The total incidence of sex-linked recessive lethal mutations was significantly increased in propylene oxide-exposed flies (4.28 percent) compared to controls (0.25 percent). The increase was observed in developing spermatocytes (broods at days 2-3) and mature sperm (broods at days 7-8).

Zamora et al. (1983) evaluated the mutagenicity of propylene oxide in the vapor phase in the *in vitro* Chinese hamster-HGPRT assay. Cells were grown on collagen gels in glass culture flasks. Medium was removed, the flasks inverted, and cold propylene oxide added. The propylene oxide was vaporized by briefly heating the bottle and the cells were incubated for 1 hour at 37°C. Propylene oxide caused a dose-related increase in mutants. At 32 µg/cm^3 (13,376 ppm), there was a 30 percent survival of cells and 88 mutants/10^6 survivors. Cells attached to glass did not survive exposure to propylene oxide in the absence of medium.

Propylene oxide was also tested for genotoxic activity in the mouse spermhead morphology test by exposing groups of 10 male C3H-He mice (10 weeks old) at 300 ppm (711 mg/m^3) for 7 hours/day for 5 days; five control groups of 10 mice each were also included. Groups of 10 mice were sacrificed at weeks 1, 3, 5, 7, and 9 postexposure. Cauda epididimides were removed and minced, and then the sperm were isolated; about 2000 sperm per mouse were scored for abnormal morphologies by microscopic examination. No statistically significant abnormalities were noted.

The same investigators tested propylene oxide for genotoxic activity using the dominant lethal test in a group of 10 male Sprague-Dawley rats exposed to propylene oxide at 300 ppm (711 mg/m^3) for 7 hours/day for 5 days; a control group of 10 males was also included. Two days after exposure, each male was caged with two virgin females of the same strain. Mating was for 5 days with a 2-day rest period, and each week, for 6 consecutive weeks, another pair of virgin females was introduced. No clear genotoxic effects were evident. Experimental groups differed from controls only in the first week of mating, but the control group had an unusually low rate of implantation when compared to subsequent control groups.

Bootman et al. (1979) tested propylene oxide in a dominant lethal test in which groups of 10 male CD-1 mice received 14 daily doses of 50 or 250 mg/kg propylene oxide by gavage; control groups received 0.5 percent gum tragacanth (vehicle control) or three daily doses of 200 mg/kg ethylmethanesulfonate (EMS). Males were then mated for 7 days with two virgin female CD-1 mice. There were six successive weekly matings. Females were sacrificed 18 days after mating initiation, and implants, early deaths, and late deaths were recorded for each female. Pregnancy rates, total implants/sire, and post-implantation loss were not different in negative control groups and propylene oxide-treated groups. Females of the positive control group had a significant reduction in pregnancy rate in weeks 2 and 5 and an increase in implant deaths after weeks 1 and 2 of mating. There was no evidence of genotoxic effects on sperm.

Bootman et al. (1979) also tested propylene oxide in the mouse micronucleus test. Groups of male CD-1 mice were administered two doses of propylene oxide by gavage at 30 and 6 hours before sacrifice or were given two doses intraperitoneally on the same schedule. The doses administered orally were 100, 250, or 500 mg/kg, and those injected intraperitoneally were 75, 150, or 300 mg/kg at each dosing. Appropriate vehicle control (0.5 percent tragacanth) and positive control (2 x 55 mg/kg cyclophosphamide) groups were included. The numbers of micronucleated cells per 10^3 polychromatic erythrocytes were scored. No effects were noted after oral administration, but there was a significant increase in micronucleated cells in mice receiving two 300-mg/kg doses of propylene oxide intraperitoneally as compared to vehicle controls.

The same investigators (Bootman et al., 1979) conducted cytogenetic studies in cultured human lymphocytes. Growing cultures were incubated for 24 hours with 1.85 or 9.25 µg/ml propylene oxide. Control cultures had sterile water added, and positive controls were incubated with 0.93 µg/ml chlorambucil. Colcemid (4 µg) was added 3 hours before cells were harvested. After harvesting, the cells were fixed and stained with Giemsa, and slides prepared for chromosomal analysis. There was a dose-related increase in the frequency of chromosomal aberrations following propylene oxide exposure. The largest increases occurred as chromatid gaps and breaks and as chromosome breaks. Propylene oxide at 9.25 µg/ml produced an incidence of aberrations similar to the positive controls (0.93 ug/ml chlorambucil) when gaps were not scored (Bootman et al., 1979).

Dean and Hodson-Walker (1979) tested the genotoxicity of propylene oxide in an *in vitro* chromosome assay utilizing rat liver epithelial cells. This system was shown not to require an extrinsic metabolic activating system. Cells were exposed to propylene oxide at concentrations between 25 and 100 µg/ml for 24 hours and treated with colcemid (0.3 µg/ml) in the final 2 hours of incubation. There was a dose-related increase in chromatid gaps (1.1, 5.3, 17.5, 31.3, and 53.7 percent at 0, 25, 50, 75, and 100 µg/ml, respectively) and in

chromatid deletions (0.3, 1.3, 3.3, and 6.0 percent at 0, 25, 50, and 75 µg/ml, respectively); however, there were no increases in chromosomal aberrations. These results strongly suggest clastogenic activity of propylene oxide.

Lynch et al. (1984b) assayed sister-chromatid exchanges (SCE's) and chromosomal aberrations in cultured lymphocytes from cynomolgus monkeys that had been exposed to propylene oxide vapors. Groups of 12 adult male monkeys were exposed to propylene oxide at 0, 100, or 300 ppm for 7 hours/day, 5 days/week for 2 years. Blood was collected in the 24th month and lymphocyte cultures established. To measure SCE's, 5-bromodeoxyuridine (50 µmol/ml BrdUrd) was added to the cultures; to measure chromosomal aberrations, BrdUrd was omitted. There were no significant increases in the incidence of SCE's or in the incidence of chromosomal aberrations in propylene oxide-exposed groups of monkeys compared to controls. In comparison, exposure of cynomolgus monkeys to ethylene oxide at 50 or 100 ppm, however, did result in a significant increase in SCE's and chromosomal aberrations. In addition, Lynch et al. (1983) also studied the spermatogenic function of these monkeys at the end of the 2-year study. Statistically significant (p value not reported) decreases in sperm counts and sperm motility and increases in drive range were seen in all treated groups of monkeys. However, no differences in the number of sperm head abnormalities were detected between exposed and control monkeys.

Tucker et al. (1986) exposed phytohemagglutinin-stimulated human peripheral lymphocyte cultures to propylene oxide at a concentration of 2.5 percent to examine the induction of SCE's. The SCE frequency was increased from 8.74 per cell in the control to 22.74 per cell in the treated cells demonstrating its genotoxicity.

2.7. CARCINOGENICITY

Walpole (1958) tested the ability of various alkylating agents to cause sarcomas at the site of injection in rats. When propylene oxide in arachis oil was injected subcutaneously in rats (sex not specified), a total dose of 1500 mg/kg given over 325 days caused injection-site sarcomas in 8 of 12 rats, whereas injection of propylene oxide in water, using the same regimen, produced sarcomas in 3 of 12 rats. It could not be determined if propylene oxide was a direct carcinogen, an initiator, or a promoter.

Dunkelberg (1981) investigated the carcinogenic potential of propylene oxide in groups of 100 female NMRI mice injected subcutaneously with 0.1, 0.3, 1.0, or 2.5 mg propylene oxide in tricaprylin once a week for 95 weeks. A positive control group (100 mice) received benzo(a)pyrene (2.5 µg/mouse) from week 32. Groups of 200 mice served as the untreated controls and vehicle controls (0.1 ml tricaprylin). There was a dose-related increase in tumors at the injection site (Table 2-3); the first tumor appeared at 39 weeks in the high-dose group. Tumors at sites away from the site of injection occurred sporadically, and their incidences were similar in control and dosed groups.

Dunkelberg (1982) tested the carcinogenicity of intragastrically administered propylene oxide in female Sprague-Dawley rats. Groups of 50 rats were administered propylene oxide in salad oil at 0, 15, or 60 mg/kg body weight 2 times a week for 150 weeks. Survival was about 60 percent in all groups at 2 years. Propylene oxide induced local tumors, primarily squamous cell carcinomas of the forestomach. In addition, there was an increase in papillomas and reactive changes in the squamous epithelium of the forestomach (Table 2-4). The first stomach tumor appeared at week 79 in the high-dose group. The incidence of tumors at sites away from the site of administration was similar in dosed and control groups.

Table 2-3. Injection Site Tumors in NMRI Mice Receiving Propylene Oxide

	Untreated controls	Vehicle controls	Propylene oxide, mg/animal				
			0.1	0.3	1.0	2.5	B(a)P[a]
No. of mice	200	200	100	100	100	100	100
No. of tumors at injection site	0	5	4	4	14	20	83
Fibrosarcoma	-[b]	4	2	2	10	13	74
Pleomorphic sarcoma	-	-	1	-	2	2	7
Lymphoma infiltrate	-	1	1	2	2	2	2
Adenocarcinoma	-	-	-	-	-	1	-
Cystic granuloma	-	-	-	-	-	2	-

[a] Benzo(a)pyrene.
[b] Data not available.
Source: Dunkelberg (1981).

Table 2-4. Incidence of Stomach Tumors and Nonneoplastic Changes in Rats Intragastrically Administered Propylene Oxide

Histologic findings	Dose, mg/kg		
	0	15	60
Squamous cell carcinoma	0	2	19
Adenocarcinoma	0	0	1
Carcinoma in situ	0	0	1
Hyperkeratosis, hyperplasia, and papilloma	0	7	17

Source: Dunkelberg (1982).

Reuzel and Kuper (1983) exposed Cpb:WU Wistar rats (100 animals/sex/group) to propylene oxide at atmospheric concentrations of 0, 30, 100, or 300 ppm for 6 hours/day, 5 days a week for 123 weeks (female) or 124 weeks (males). After 12, 18, and 24 months, 10 rats/sex/group were sacrificed for interim information. No differences in site, type, or incidences of tumors were found between the groups at any of the interim sacrifices. However, an increased incidence in mammary gland tumors was noted in exposed females at the terminal sacrifice (Table 2-5). There was a dose-related increase in multiple fibroadenomas (statistically significant trend using Cox's time-to-tumor analysis) and a significant increase in the number of females with total fibroadenomas or carcinomas at 300 ppm when compared to controls. There were no tumors in the nasal turbinates, although there was a dose-related increase in focal hyperplasia. Incidences of tumors at other sites were similar between exposed and control groups of males and females. The authors

suggested that propylene oxide was not a direct acting carcinogen but, rather, it "enhanced the development of malignant neoplasms by an indirect mechanism such as immunosuppression or disturbed hormonal balance."

Lynch et al. (1984a) tested the carcinogenicity of inhaled propylene oxide in male Fischer 344 rats. Groups of 80 rats were exposed to 0, 100, or 300 ppm propylene oxide vapor for 6.9 hours (average)/day, 5 days/week for 2 years (488 days of exposure). There was a statistically significant increase in the incidence of pheochromocytomas of the adrenal glands (25 of 78 and 22 of 80 at 100 and 300 ppm, respectively, compared to 8 of 73 in controls) but no dose-related trend. Two adenomas of the nasal passages were found at 300 ppm and none at 100 ppm or in controls. No increases in other respiratory tract neoplasms were noted. There was, however, a statistically significant increased incidence of epithelial hyperplasia in the nasal cavities of rats exposed to propylene oxide at 300 ppm (11 of 78) compared to controls (0 of 76).

The finding of increased proliferative lesions was stated by the authors to be similar to that of a bioassay performed by the National Toxicology Program (1985) and Renne et al. (1986). In this bioassay, F344/N rats and $B6C3F_1$ mice were exposed to propylene oxide vapors at concentrations of 200 or 400 ppm, 6 hours/day, 5 days/week for 2 years. The rats tolerated the exposure with no increase in mortality when compared to controls. In the high-dose group, 58 percent of the males and 62 percent of the females survived until study termination. The terminal mean body weights of males and females exposed at 400 ppm were 8 and 6 percent lower than those of the controls, respectively.

In female rats, "some evidence" of compound-related carcinogenicity was reported based on a positive trend ($p < 0.04$) in papillary adenomas of the nasal cavity (Table 2-6). There were also dose-related increases in inflammatory and preneoplastic lesions in the nasal cavities of both males and females. The epithelial hyperplasia lesions were morphologically similar but less focal than the papillary adenomas. In addition, there was an increased incidence of thyroid C-cell adenomas and C-cell carcinomas in females receiving 400 ppm; however, only the combined incidence of these tumors was significantly different from that of the controls (Table 2-7). The combined incidence of endometrial stromal polyps or sarcomas of the uterus was increased in the dosed groups, but the incidence in the concurrent controls was low compared to historical controls.

In addition, dose-related increases in the following nonneoplastic lesions were observed: in male rats, acinar cell atrophy of the pancreas (1 of 47, 12 of 49, and 17 of 47) and testicular atrophy (18 of 49, 40 of 50, and 24 of 50) in the control, low, and high-dose groups, respectively; and in female rats, cytomegaly of the adrenals (1 of 48, 6 of 49, and 11 of 48) in the control, low, and high-dose groups, respectively.

In mice, a significant increase in mortality occurred in the dosed animals. Survival at the high dose was 58 percent in males and 20 percent in females compared to 84 and 54 percent for the controls, respectively. The terminal mean body weights of males and females exposed at 400 ppm were 21 and 10 percent lower than those of the controls, respectively.

The incidence of histopathologic lesions in the nasal cavities of mice is summarized in Table 2-8. Based on the increased incidences of hemangiomas and hemangiosarcomas in the nasal cavities, propylene oxide can be considered a site-specific carcinogen. Inflammation of the respiratory epithelium was observed, but no significant hyperplasia or metaplasia was noted. There was also an increased incidence of mammary gland adenocarcinomas (3 of 50 and 3 of 50 at 200 and 400 ppm, respectively, compared to 0 of 50 in the controls); this increase was not statistically

Table 2-5. Incidence of Mammary Gland Tumors in Female Rats Exposed to Propylene Oxide Vapor[a]

	Exposure level, ppm			
	0	30	100	300
Fibroadenoma Single	25	11	15	13
Fibroadenoma Multiple	7	19[b]	23[b]	33[b]
Fibroadenoma Total	32	30	39	47[c]
Adenoma	0	0	0	1
Fibroma	0	0	1	2
Carcinoma (tubulopapillary)	3	6	5	8[c]

[a] Tumor incidences are based on examination of all tissues of control and high-dose groups and all gross lesions of low and mid-dose groups. Fifty animals/ sex/group were examined, excluding animals at the interim sacrifice.
[b] Statistically significant trend using a chi-square test.
[c] Statistically significant ($p < 0.05$) using Cox's test adjusting for time to tumor.
Source: Reuzel and Kuper (1983).

Table 2-6. Incidence of Nasal Cavity Lesions in Rats Exposed to Propylene Oxide via Inhalation[a]

	Males Exposure level, ppm			Females Exposure level, ppm		
Type of lesion	0	200	400	0	200	400
Suppurative inflammation	9	21	38	3	5	23
Epithelial hyperplasia	0	1	11	1	0	5
Squamous metaplasia	1	3	21	1	2	11
Papillary adenoma	0	0	2	0	0	3

[a] Tissues from 50 animals were examined histologically in each group.
Source: NTP (1985).

significant but showed a significant positive trend. An increased incidence of atrophy of the ovary was also noted (8 of 46 and 20 of 37 at 200 and 400 ppm, respectively, compared to 6 of 40 in the controls).

From the available data, NTP concluded that propylene oxide showed clear evidence of carcinogenicity in mice and some evidence of carcinogenicity in rats.

The International Agency for Research on Cancer (1985) has evaluated that there is sufficient evidence for the carcinogenicity of propylene oxide for experimental animals but inadequate evidence for the carcinogenicity of propylene oxide for humans. According to EPA's guidelines for classifying carcinogenic evidence (Federal Register, 1986), propylene oxide would be

Table 2-7. ***Incidence of Thyroid Lesions in Female Rats Exposed to Propylene Oxide via Inhalation***

Type of lesion	Exposure level, ppm		
	0	200	400
No. of tissues examined	45	35	37
C-cell hyperplasia	7	6	5
C-cell adenoma	1	1	4
C-cell carcinoma	1	1	3
Adenoma and carcinoma	2	2	7[a]

[a] *Statistically significant ($p < 0.05$) compared to controls.*

Source: National Toxicology Program (1985).

tentatively placed in the B-2 category (Probable Human Carcinogen) because of positive animal data and an absence of epidemiological studies (Paynter, 1985).

Preliminary unit risk estimation for the carcinogenicity of propylene oxide for both the gavage and inhalation routes of exposure has been performed by the EPA (U.S. Environmental Protection Agency, 1985). The q_1^* values were calculated using the linearized multistage model of Crump based on the tumor response data for Sprague-Dawley rats in the gavage study of Dunkelberg (1982) or based on the tumor response data on $B6C3F_1$ male mice in the National Toxicology Program (1985) inhalation study. The q_1^* value is a 95 percent upper confidence limit which is taken as an upperbound estimate of the human cancer potency of the chemical -- the true risk is not likely to be higher than the estimate, but it could be smaller (Federal Register, 1980). The pertinent data for the calculations are summarized in Table 2-9. Calculated values for q_1^* are presented in Table 2-10. Potency, mg/kg/day, has been converted to a $\mu g/m^3$ basis for air concentration. It will be noted that the inhalation estimate, $3.74 \times 10^{-6}(\mu g/m^3)^{-1}$, is approximately twentyfold lower than that calculated for the ingestion data, $6.83 \times 10^{-5}(\mu g/m^3)^{-1}$. There are insufficient data on pharmacokinetics to evaluate if the assumption of 50 percent absorption used in the calculations is reasonable. For air unit risk estimates, it may be preferable to calculate the value from the inhalation study; however, it also may be preferable to use the less conservative estimate from the gavage study. These are only rough estimates to be used as tools for further preliminary evaluations and should not be construed as Agency policy.

2.3. TERATOGENICITY AND REPRODUCTIVE EFFECTS

Hardin et al. (1983a) conducted a teratogenicity study with rats and rabbits exposed to propylene oxide by inhalation and concluded that propylene oxide was embryotoxic but not teratogenic. The study groups consisted of 32-45 sexually mature female Sprague-Dawley rats that were sperm positive and 23-30 New Zealand white rabbits that were artificially inseminated. Groups of animals were exposed in a dynamic inhalation chamber at 500 ppm (1118

Table 2-8. Incidence of Nasal Cavity Epithelial Lesions in Mice Exposed to Propylene Oxide via Inhalation[a]

	Males Exposure level, ppm			Females Exposure level, ppm		
Type of lesion	0	200	400	0	200	400
Serous inflammation	0	13[b]	2	2	6	2
Suppurative inflammation	0	8	4	0	16[b]	23[b]
Acute/chronic inflammation	1	14[b]	38[b]	0	14[b]	18[b]
Squamous metaplasia	0	1	0	0	0	2
Papilloma	0	0	1	0	0	0
Squamous cell carcinoma	0	0	1	0	0	0
Adenocarcinoma	0	0	0	0	0	2
Hemangioma	0	0	5[b]	0	0	3
Hemangiosarcoma	0	0	5[b]	0	0	2
Hemangioma and hemangiosarcoma	0	0	10[b]	0	0	5[b]

[a] Tissues from 50 animals were examined histologically in each group.
[b] Statistically significant ($p < 0.05$) compared to controls.
Source: National Toxicology Program (1985).

mg/m3) propylene oxide for 7 hours/day. Rats were exposed in one of three time periods: for 3 weeks prior to mating and throughout gestation, on days 1-6 of gestation, or on days 7-16 of gestation. All rats were sacrificed on day 21 of gestation. Groups of rabbits were exposed on days 1-6 or 7-19 of gestation and sacrificed on day 30. Control groups of animals were exposed to filtered air. All rat and rabbit fetuses were examined for external defects, and half of the fetuses were examined for brain defects.

There was no maternal mortality in either rats or rabbits. However, a statistically significant decrease in body weight gain and a significant increase in kidney-to-body weight ratios was observed in exposed rats when compared with control animals. Similar increases in the relative weights of the lungs, liver, and spleen of rats were observed, but the increases were not statistically significant. The effect on relative organ weights was greater in the group exposed for 3 weeks prior to mating and through gestation than in groups exposed during gestation only. There was no effect on body or organ weights in rabbits. A significant ($p < 0.01$) decrease in the numbers of corpora lutea, implants, and live fetuses in rats exposed to propylene oxide for 3 weeks prior to mating was noted when compared to the other exposed groups or controls. There was a significant increase in the number of resorptions in rats exposed from days 7-16 of gestation but not in other exposed groups when compared to controls.

Table 2-9. Data for Derivation of q_1^*

Reference	Dunkelberg (1982)	NTP (1985)
Route, vehicle:	gavage, salad oil	inhalation
Species, strain, sex:	rat/Sprague-Dawley/female	mouse/B6C3F$_1$/ male
Body weight (assumed):	0.35 kg	0.030
Length of exposure:	1029 days	721 days
Length of experiment:	1050 days	721 days
Lifespan of animal:	1050 days	721 days
Tumor site and type:	forestomach, squamous cell carcinoma	nasal cavities: hemangioma or hemangio-sarcoma
Experimental doses	**Transformed doses (mg/kg/day)**	**Tumor incidence**
Gavage (219 doses)		
60 mg/kg/day	10.28	19/50
15 mg/kg/day	2.58	2/50
0.0 mg/kg/day	0.0	0/100[a]
Inhalation (6 hours/day, 5 days/week)		
400 ppm	110[b]	10/50
200 ppm	55[b]	0/50
0.0 ppm	0.0	0/50

[a] Combined vehicle and untreated control.
[b] Assumes 50 percent absorption.
Source: U.S. Environmental Protection Agency (1985).

Table 2-10. Calculated q_1^* Values for Propylene Oxide

Parameter	Units	Gavage study	Inhalation study
Unadjusted q_1^*	$(mg/kg/day)^{-1}$	4.08×10^{-2}	9.84×10^{-4}
Human q_1^*	$(mg/kg/day)^{-1}$	$2.39^a \times 10^{-1}$	$1.31^b \times 10^{-2}$
Human q_1^*	$(\mu g/m^3)^{-1}$	$6.83^c \times 10^{-5}$	3.74×10^{-6}

[a] Unadjusted $q_1^* \times (70/0.35)^{1/3}$.
[b] Unadjusted $q_1^* \times (70/0.030)^{1/3}$.
[c] Human q_1^* $(mg/kg/day)^{-1} \times (2.86 \times 10^{-4}\ m^3/kg) \times (10^{-3}\ \mu g/mg)$, assuming 70 kg the average human weight and 20 m^3 the daily respiratory volume.

Fetal body weight and crown-to-rump length were significantly reduced in all propylene oxide-exposed rats. There was an increased incidence of rib dysmorphology (wavy ribs) and decreased skeletal ossification. No embryonic, fetotoxic, or developmental defects were noted in rabbits.

2.9. NEUROTOXICITY

Groups of 12 male monkeys (*Macaca fascicularis*) were exposed to propylene oxide at 0, 100, and 300 ppm for 6 hours/day, 5 days/week for 24 months and tested bimonthly for nerve conduction velocity (Sprinz et al., 1982). At the end of the exposure period, two monkeys from each group were deeply anesthetized and perfused with fixative. Brains, spinal cords, and ulnar and sciatic nerves were removed, placed in fixative, and prepared for microscopic examination. No differences were found between exposed animals and controls in sections at various levels of the sciatic and ulnar nerves or eight segments of the spinal cord. There were signs of axonal dystrophy in the area of the nucleus gracilis and fasciculares gracilis in the medulla oblongata of the brain in monkeys exposed at 300 ppm. No demyelination was found in monkeys exposed to propylene, while demyelination was observed in the distal fasciculus gracilis in two of four monkeys exposed to ethylene oxide. The authors suggested that additional studies are needed to establish whether neurotoxic effects result from propylene oxide exposure.

2.10. EFFECTS ON HUMANS

Two case reports involving contact dermatitis resulting from exposure to propylene oxide were found in the literature. Van Ketel (1979) described the case of a female electron microscopy technician who had eczema on her hands for 8 months. A standard patch test gave a clear positive reaction to propylene oxide. In a control group of 16 persons, only one had a positive reaction to propylene oxide; this person had also had previous daily contact with the chemical. Jensen (1981) reported two cases of contact dermatitis in laboratory assistants who had used a commercial disinfecting swab containing 1 percent propylene oxide. Standard patch tests given to these individuals yielded positive responses to propylene oxide (0.1, 0.5, and 1 percent in ethanol), while a control group of 25 people gave no positive responses. The results of these case studies indicate that propylene oxide can initiate dermatitis in susceptible individuals after repeated exposure, but is unlikely to do so in the general population.

Thiess et al. (1981) studied chromosomal aberrations in the lymphocytes of a group of 43 men who worked in ethylene oxide manufacturing or processing plants and were concurrently exposed to propylene oxide. Data on exposure levels were not presented, although it was stated that the concentration of ethylene oxide was below 5 ppm under normal conditions (i.e., nonbreakdown) and propylene oxide levels were 1 ppm or less. The percentage of lymphocytes with aberrant chromosomes (including and excluding gaps) was significantly increased for those workers with more than 20 years of exposure over the control percentage. Statistically significant changes were not found in groups of workers with: (1) less than 20 years' exposure, (2) less than 20 years' exposure plus one high exposure to ethylene oxide caused by an accident, and (3) a single exposure to ethylene oxide due to an accident. However, a conclusion cannot be made on the possible mutagenic effects of propylene oxide in humans based on this study for two reasons: First, the only group showing an increased frequency of aberrant chromosomes also had multiple, and possibly long-term, exposure to a variety of potential mutagens including ethylene

oxide, a known human mutagen. Second, the mean age of this group was 52.5 years while the mean age of the control group was only 38.6 years.

Pero et al. (1982) investigated unscheduled DNA synthesis (DNA repair) in the lymphocytes of workers exposed to propylene oxide for an average of 10 years. The study group was composed of 23 workers, ages 25-59 years (mean 41 years), who were exposed to propylene oxide in a factory producing alkylated starch. Estimates of exposure were obtained using personal and stationary sampling; the time-weighted average was 0.6-12 ppm for 2-6 hours per day. The control group consisted of 12 workers, ages 21-46 years (mean 30 years). Unscheduled DNA synthesis (UDS) was measured by exposing cultured lymphocytes to a standardized dose of N-acetoxy-2-acetylaminofluorene (NA-AAF) and measuring thymidine incorporation. This value was adjusted for individual variation by dividing it by the level of NA-AAF binding to DNA as concurrently measured in each individual's lymphocytes. The NA-AAF-induced UDS was significantly lower ($p < 0.001$, t-test) in the propylene oxide-exposed group, thus indicating that these individuals had a reduced capacity to repair DNA damage.

Van Sittert and De Jong (1985) conducted a prospective study of chromosome aberrations in the lymphocytes of plant workers exposed to propylene oxide. Precise data on levels of exposure were utilized in this study of 116 men and 20 controls. The authors concluded that changes in the frequency of chromosome aberrations in the lymphocytes during the period of 1978-81 were unlikely of occupational origin. They also note that the low levels under study (below 1 ppm, 8-hour TWA) may be such that the method is not sensitive enough to detect differences at such levels.

Thiess et al. (1982) carried out a retrospective cohort study of 602 employees in eight German production plants where alkylene oxides (ethylene oxide and propylene oxide) and their derivatives were produced. Mortality of these employees was compared with that in three subsets of the German population. Overall, 56 deaths were observed in the study cohort, compared with 71.5-76.6 expected in the reference populations. No deaths occurred in any cancer category that were significantly higher than those expected. Malignant diseases occurred in men who worked in different production areas. However, exposure to butylene oxide, dioxane epichlorohydrin, dichloropropane, and other chemicals also existed.

3. Summary and Conclusions

Propylene oxide is an epoxyalkane with a high water solubility and a high vapor pressure. Its major use is as an intermediate in the production of polyurethane foams and propylene glycol. It is also used as a fumigant and as a pesticide.

Of the estimated 1.77 billion pounds of propylene oxide produced annually, 1.3 million pounds is released to the atmosphere. Average atmospheric concentrations at a distance of 20 km or greater from production facilities are estimated to be less than 0.0001 ppt (10^{-7} ppb). Occupational exposures are believed to be less than 1 ppm. Propylene oxide has been detected in fumigated foods and plastics.

Propylene oxide is expected to be very mobile in the environment and is not expected to bioconcentrate or bioaccumulate. The calculated atmospheric half-life is 6.1 days. The estimated hydrolysis half-life in water ranges from 7 to 12 days.

The reported ecological effects of propylene oxide are limited to acute toxicity studies. The reported LC_{50} values in fish range from 89 to 215 mg/l. No chronic or life-cycle effects have been reported.

No studies were found in the available literature on the absorption, distribution, metabolism, or excretion of propylene oxide. However, based on available data on structurally similar compounds such as propylene and epichlorohydrin, it appears that propylene oxide is likely to be readily absorbed through the gastrointestinal and respiratory tracts and distributed to the kidneys, liver, pancreas, adrenals, and spleen. Metabolism may involve conjugation with glutathione or hydrolysis by epoxide hydrase. Excretion of propylene oxide and its metabolites is expected to be primarily through the urine and expired air. Several studies were found on the ability of propylene oxide to alkylate protein, nucleotides, and DNA *in vitro* and *in vivo*.

The oral LD_{50} for propylene oxide was reported to be in a range of 0.52 to 1.14 g/kg in rats and 0.66 to 0.69 g/kg in guinea pigs. The LC_{50} for a 4-hour inhalation exposure was from 7697 to 9486 mg/m^3 in rats and from 2420 to 4126 mg/m^3 in mice. The LC_{LO} for a 4-hour inhalation exposure was 9486 mg/m^3 in pigs and 4750 mg/m^3 in dogs.

Acute exposure to sublethal concentrations of propylene oxide vapor caused eye and respiratory tract irritation in experimental animals. The lowest concentrations at which effects were seen in experimental animals with acute or subchronic inhalation exposures were in the range of approximately 400-500 ppm propylene oxide. Skin contact with an undiluted or 10 percent solution of propylene oxide caused skin irritation in rabbits.

Exposure of rats to propylene oxide at 100 or 300 ppm (270 or 711 mg/m^3) for 2 years caused a statistically significant decrease in body weight gain and increased mortality. There was also an increased incidence of inflammatory lesions of the lungs, nasal cavity, and trachea. The no-observed-adverse-effects level for prolonged repeated 6- to 7-hour daily exposure is 70 mg/m^3 (29 ppm).

Propylene oxide was found to be a direct acting mutagen, causing base-pair substitutions in *Salmonella* (0.04-1.0 mg/ml) and *Escherichia coli* strains. It

was also found to produce forward mutations in the yeast *Schizosaccharomyces pombe* and reverse mutations in the bacterium *Klebsiella pneumoniae* and the fungus *Neurospora crassa*. It was a positive mutagen in the *Drosophila* sex-linked recessive lethal test. No clear genotoxic effects were reported using the dominant lethal test in rats (inhalation, 300 ppm) or mice (oral, 50 mg/kg). When given to mice by the intraperitoneal route (but not by the oral route), propylene oxide (two 300-mg/kg doses) caused an increase in micronuclei in polychromatic erythrocytes. It was clastogenic in cultured human lymphocytes, causing chromosomal aberrations. In monkeys exposed to levels of 100 or 300 ppm for 2 years, propylene oxide did not induce sister-chromatid exchanges or chromosomal aberrations in the lymphocytes and did not increase the frequency of abnormal sperm head morphology, but caused a decrease in sperm counts and motility.

Repeated subcutaneous injections of propylene oxide (1 mg/kg) caused sarcomas at the injection site in rats and mice; repeated intragastric administration (60 mg/kg) induced carcinomas and reactive changes in the epithelium of the forestomach of rats. No clear oncogenic effects were noted when rats were exposed by inhalation at 100 or 300 ppm propylene oxide over their life time. There was an increased incidence of adrenal pheochromocytomas at both exposure levels but no dose-related trend. Two adenomas were also found in the nasal passages of rats exposed to propylene oxide at 300 ppm, whereas none was found in the controls. However, there was a dose-related increase in complex hyperplasia of the nasal cavities. A significant increase in the number of female Cpb:WU Wistar rats with total mammary gland fibroadenomas or carcinomas when compared to controls was reported in animals exposed to propylene oxide at 300 ppm, 6 hours/day, 5 days a week for 123 weeks. However, it was suggested that propylene oxide enhanced the development of malignant neoplasms rather than acting as a direct carcinogen.

In an NTP carcinogenicity study with F344/N rats and $B6C3F_1$ mice exposed to propylene oxide vapors at concentrations of 200 or 400 ppm, 6 hours/day, 5 days/week for 2 years, it was concluded that propylene oxide showed clear evidence of carcinogenicity in mice and some evidence of carcinogenicity in rats. This conclusion was based on the following findings: a significant increase in the incidence of hemangiomas and hemangiosarcomas in the nasal cavities of mice exposed to the high dose and a significant positive trend in the incidence of papillary adenomas and epithelial hyperplasia in the nasal cavities of female rats.

According to EPA's Guidelines for Carcinogen Risk Assessment (Federal Register, 1986), propylene oxide would be tentatively placed in the B-2 weight-of-evidence category because of positive animal data and an absence of epidemiological studies.

Propylene oxide was found to be embryotoxic but not teratogenic in rats and rabbits exposed at 500 ppm prior to and during gestation. One study indicated that chronic exposure to propylene oxide may cause some neuropathologic changes in monkeys.

Two case reports indicated that contact dermatitis can result from short-term human exposure to high levels of propylene oxide. An epidemiology study with workers occupationally exposed to propylene oxide indicated that the ability of the lymphocytes to repair chemically induced DNA damage (unscheduled DNA synthesis) was significantly lower than that of the control group; however, the relationship of this reduction in repair proficiency to human health is unclear.

Only limited information was found in regard to air concentrations of propylene oxide. These indicated typical annual average ambient air concentrations of ≤1 ppt. However, no data were available on short-term ambient concentrations of ≤1-3 hours' duration or maximum 24-hour levels against which to compare observed effect levels for acute or subchronic health effects, and no data were found on concentrations at or proximal to plant lines around industrial facilities emitting the substance. Also, it remains to be determined as to what level (or upper bound) of carcinogenic risk might be estimated to be associated with observed or modeled air concentrations of propylene oxide.

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